Naeye and Peters (1984) investigated the mental development of smokers' children by comparing siblings whose mothers smoked in one but not in subsequent pregnancies and found that hyperactivity, short attention span, and lower scores on spelling and reading tests were more frequent for the children whose mother had smoked during pregnancy, but the differences were relatively small, the test scores being only 2 to 4 percent lower. Dunn also studied neurological and electroencephalographic abnormalities among 6-year-old children of smokers and found these conditions to be slightly more common in the children of mothers who had smoked during pregnancy, but again the differences were not statistically significant. Small sample sizes in many of these studies and the relative infrequency of the events of interest limit interpretation of the studies (Dunn et al. 1977).

Peptic Ulcer

The 1964 Surgeon General's Report noted an association between peptic ulcer and cigarette smoking. The 1979 Report stated that the relationship between cigarette smoking and peptic ulcer is significant enough to suggest a causal relationship. Peptic ulcer disease is more likely to occur, less likely to heal, and more likely to cause death in smokers than in nonsmokers.

Cigarette smoking retards the healing of peptic ulcer (Sontag et al. 1984; Lane and Lee 1988; Korman et al. 1983). A large trial of cimetidine, a drug used in the treatment of peptic ulcer, was reported in 1984 by Sontag and associates. Ulcer recurrence was much more frequent among smokers compared with nonsmokers for both the placebo- and the cimetidine-treated groups.

Nicotine decreases pyloric sphincter pressure and therefore permits increased reflux of duodenal contents into the stomach. Nicotine also decreases pancreatic bicarbonate secretion. This may impair neutralization of gastric acid in the duodenum, contributing to the formation and persistence of duodenal ulcers. Smoking cessation probably reduces the incidence of peptic ulcer and is an important component of peptic ulcer treatment even with the available effective drug therapy.

Osteoporosis

The 1964 Report did not discuss osteoporosis. The interest in osteoporosis is fairly recent because of the increasing number of older individuals, especially women, at risk of fracture; the better methods of measuring bone mineral mass; and the understanding of osteoporosis pathophysiology and risk factors.

Osteoporosis leading to fractures, especially of the hip, wrist, and spine, is an important cause of disability and death, predominantly among postmenopausal women. About 15 to 20 million persons in the United States have osteoporosis. Each year about 1.3 million fractures are attributed to this disease (Journal of the American Medical Association 1984).

Smoking may be a risk factor for osteoporosis (Willett et al. 1983). Women smokers have an earlier age of menopause, an important risk factor for osteoporosis (Willett et al. 1983). Smokers may have a lower intake of calcium during adolescence and young

adult life when maximum bone mineral mass is reached (Sandler et al. 1985). Smokers also weigh less than nonsmokers (US DHHS 1988). Obesity substantially reduces the risk of hip fracture (Kiel et al. 1987). Overweight women have higher endogenous estrogen levels and greater bone mass (Cauley et al. 1986). Exogenous estrogen intake among postmenopausal women results in a decreased risk of fracture (Ernster et al. 1988). Women who smoke and are on estrogen therapy may have reduced levels of estrogens in their blood compared with levels for nonsmoking women. Among women who smoked and were given high doses of estradiol, blood levels of estrone and estradiol were only one-half of those among nonsmokers (Jensen, Christiansen, Rodbro 1985). Increased hepatic metabolism of exogenous oral estrogen may result in lower estrogen levels among postmenopausal cigarette smokers.

Several case–control studies have evaluated the relationship between osteoporosis and cigarette smoking. Most find an increased risk of fractures among smokers. However, problems with study design, especially the potential effects of confounders such as obesity and age, have limited the interpretation of these studies, as have contradictory findings. For example, a large study of hip fractures among postmenopausal women in four Connecticut hospitals did not find any differences in risk between smokers and nonsmokers (Kreiger et al. 1982). A study in Iowa by Sowers (Sowers, Wallace, Lemke 1985) of 86 women aged 20 to 35 years did not find any relationship between forearm bone mineral mass and smoking during maximal bone mineralization. A study in Denmark (Jensen 1986) compared bone mineral content among 77 long-term smokers and 103 nonsmokers. Bone mineral content correlated with fat mass. For the same degrees of obesity, smokers did not have any lower level of bone mineral content than nonsmokers. The results of these studies suggest that the effect of smoking as a risk factor for osteoporosis and fracture among postmenopausal women may be primarily determined by the inverse relationship between smoking and obesity. It is possible that the early age of menopause among smokers may also contribute to the risk of osteoporosis.

Involuntary Smoking

The issue of involuntary smoking was not raised in the 1964 Surgeon General's Report. The first report of the Surgeon General to address the possible health effects of involuntary smoking was published in 1972 (US DHEW 1972). Over the ensuing 15 years, evidence on the adverse consequences of involuntary smoking began to amass, with several hundred papers being published. In 1986, the Surgeon General's Report (US DHHS 1986a) focused exclusively on this subject.

Nonsmoking adults exposed to ETS have a higher frequency of symptomology, such as eye irritation and upper respiratory symptoms (US DHHS 1986a). The relationship between lung cancer among nonsmokers and ETS has been documented in both case–control and longitudinal studies. Most of these studies have measured the increased risk of lung cancer among nonsmoking women, usually wives exposed to their husbands' tobacco smoke. A 1.3-fold increased risk of lung cancer has been estimated from these studies and is consistent with the amount of exposure to carcinogens from

ETS (US DHHS 1986a), the duration of exposure, and the differences in the distribution of potential carcinogens between sidestream and mainstream smoke.

The 1986 Surgeon General's Report on involuntary smoking concluded (US DHHS 1986a):

1. Involuntary smoking is a cause of disease, including lung cancer, in healthy nonsmokers.
2. The children of parents who smoke compared with the children of nonsmoking parents have an increased frequency of respiratory infections, increased respiratory symptoms, and slightly smaller rates of increase in lung function as the lung matures.
3. The simple separation of smokers and nonsmokers within the same airspace may reduce, but does not eliminate, the exposure of nonsmokers to ETS.

Another major review on involuntary smoking was released in 1986 by the National Research Council (NRC). This report concluded that the risk of lung cancer is approximately 30 percent higher for nonsmoking spouses of smokers than it is for nonsmoking spouses of nonsmokers (NRC 1986).

Since release of the 1986 Surgeon General's Report, five additional studies examining ETS exposure and lung cancer in nonsmokers have been published (Brownson et al. 1987; Dalager et al. 1986; Humble, Samet, Pathak 1987; Gao et al. 1987; Pershagen, Hrubec, Svensson 1987). All five noted a correlation between ETS exposure and lung cancer among nonsmokers. Thus, of the 16 epidemiologic studies in the scientific literature, 14 have noted a positive association.

Smokeless Tobacco

In 1979 the Surgeon General's Report included, for the first time, a review of the health consequences of using smokeless tobacco (snuff and chewing tobacco) (US DHEW 1979). In 1986, a special Surgeon General's Report, *The Health Consequences of Using Smokeless Tobacco* (US DHHS 1986b), reviewed smokeless tobacco in depth and concluded that it can cause cancer in humans. The relationship between smokeless tobacco use and cancer is strongest for the use of snuff and for cancer of the oral cavity. Smokeless tobacco can also cause oral leukoplakia, which may progress to neoplastic transformation with continued use of smokeless tobacco.

Addiction to Smoking

The 1964 Surgeon General's Report referred to tobacco use as habituating. Fifteen years later, the 1979 Report concluded that smoking was "the prototypical substance abuse dependency" (US DHEW 1979). The entire 1988 Report (US DHHS 1988) was dedicated to an exhaustive review of tobacco use as an addiction. The 1988 Report concluded:

1. Cigarettes and other forms of tobacco are addicting.
2. Nicotine is the drug in tobacco that causes addiction.
3. The pharmacologic and behavioral processes that determine tobacco addiction are similar to those that determine addiction to drugs such as heroin or cocaine.

These findings are discussed in greater detail in Part II of Chapter 5 on determinants of smoking behavior.

PART II. THE PHYSICOCHEMICAL NATURE OF TOBACCO

The 1964 Surgeon General's Report on Smoking and Health (US PHS 1964) gave impetus to intensified investigations on the physicochemical nature and composition of tobacco smoke and the identification of biologically active agents in tobacco and tobacco smoke and their modes of action.

In 1936 Brückner listed 120 known components in tobacco smoke. This number grew to about 450 in 1959 (Johnstone and Plimmer 1959), to about 950 in 1968 (Stedman 1968), to 3,875 in 1982 (Dube and Green 1982), and to 3,996 in 1988 (Roberts 1988). Today, the estimated number of known compounds in tobacco smoke exceeds 4,000, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic (US DHEW 1979; US DHHS 1983). Such diverse biological effects of cigarette smoke constituents provide a framework for understanding the multiple adverse consequences of smoking.

Since about 1960, both the composition of cigarette tobacco and the components and shape of the cigarette itself have undergone significant changes that effected reductions in standardized measurements of tar, nicotine, and other toxic agents in the smoke (Norman 1982). Perhaps the greatest advances have been made in understanding the pharmacology and toxicology of nicotine (Benowitz 1986; US DHHS 1988) and in delineating the nature and mode of action of the major carcinogens in tobacco smoke (US DHHS 1982; Hoffmann and Hecht, 1989).

Processed, unadulterated tobacco contains at least 2,550 known compounds (Dube and Green 1982). The bulk of the dried tobacco consists of carbohydrates and proteins. Other important constituents are alkaloids (0.5 to 5 percent), with nicotine as the predominant compound (90 to 95 percent of total alkaloids), and terpenes (0.1 to 3 percent), polyphenols (0.5 to 4.5 percent), phytosterols (0.1 to 2.5 percent), carboxylic acids (0.1 to 0.7 percent), alkanes (0.1 to 0.4 percent), and alkali nitrates (0.01 to 5 percent). In addition, tobacco contains traces of aromatic hydrocarbons, aldehydes, ketones, amines, nitriles, N- and O-heterocyclic compounds, pesticides, and more than 30 metallic compounds (Wynder and Hoffmann 1967; US DHEW 1979).

The composition of the processed tobacco in cigarettes influences the chemistry and toxicity of the smoke. Cigarettes manufactured in the United States are made with blends of bright, burley, and oriental tobaccos that generate weakly acidic mainstream smoke (pH 5.5 to 6.2) in which nicotine occurs in protonated form in the particulate matter. The sidestream smoke (SS) of these cigarettes is neutral to alkaline (pH 6.5 to 8.0), and part of the nicotine in SS is present in unprotonated form in the vapor phase (Brunnemann and Hoffmann 1974). These observations are important because unprotonated nicotine is readily absorbed through the buccal mucosa (US DHHS 1988).

The 400 to 500 mg of mainstream smoke (MS) freshly emerging from the mouthpiece of a cigarette is an aerosol containing about 10^{10} particles per mL; these range in diameter from 0.1 to 1.0 μm (mean diameter 0.2 μm) and are dispersed in a vapor phase (Ingebrethsen 1986). About 95 percent of the MS effluents of a nonfilter cigarette are composed of 400 to 500 individual gaseous compounds with nitrogen, oxygen, and

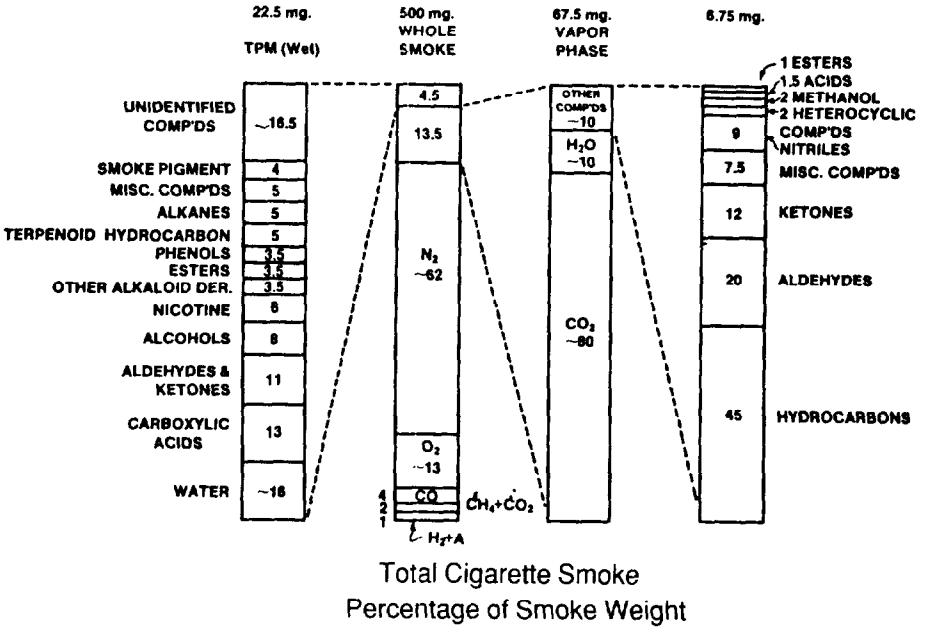

FIGURE 13.—Composition of cigarette mainstream smoke
SOURCE: Dube and Green (1982).

carbon dioxide as major constituents; the particulate matter of MS contains at least 3,500 individual compounds (Figure 13. Dube and Green 1982).

Like all organic combustion products, tobacco smoke contains free radicals, highly reactive oxygen- and carbon-centered types in the vapor phase, and relatively stable radicals in the particulate phase. The principal of the latter appears to be a quinone/hydroquinone complex capable of reducing molecular oxygen to superoxide, and, eventually, to hydrogen peroxide and hydroxyl radicals (Nakayama, Kodama, Nagata 1984; Church and Pryor 1985).

For chemical analysis, the smoke is arbitrarily separated into vapor and particulate phases. Those smoke components of which more than 50 percent appear in the vapor phase of fresh MS are considered volatile smoke constituents; all others are particulate phase components (Figure 13). Tables 5 and 6 list the major types of components identified and their estimated concentration in the smoke of one cigarette (US DHHS 1982; Hoffmann and Hecht 1989). The quantitative data presented here were obtained by machine smoking of cigarettes under standardized laboratory conditions using the method of the Federal Trade Commission (Pillsbury et al. 1969); therefore, the data do not fully reflect the human setting. This applies especially to smokers of low-yield cigarettes who tend to compensate for the low nicotine delivery by drawing smoke more intensely and inhaling more deeply (US DHHS 1988).

Table 6 does not contain information about the nature and concentration of at least 30 metals in the smoke. These compounds are not listed because less than 1 percent of the metals in tobacco are transferred into the smoke and constitute together only ≤80 µg/g(Jenkins, Goldey, Williamson 1985). Tables 5 and 6 also lack descriptions of the

TABLE 5.—Major constituents of the vapor phase of the mainstream smoke of nonfilter cigarettes

Compound[a]	Concentration/cigarette
Nitrogen	280–320 mg (56–64%[b])
Oxygen	50–70 mg (11–14%[b])
Carbon dioxide	45–65 mg (9–13%[b])
Carbon monoxide	14–23 mg (2.8–4.6%[b])
Water	7–12 mg (1.4–2.4%[b])
Argon	5 mg (1.0%[b])
Hydrogen	0.5–1.0 mg
Ammonia	10–130 µg
Nitrogen oxides (NO_x)	100–600 µg
Hydrogen cyanide	400–500 µg
Hydrogen sulfide	20–90 µg
Methane	1.0–2.0 mg
Other volatile alkanes (20)	1.0–1.6 mg[c]
Volatile alkenes (16)	0.4–0.5 mg
Isoprene	0.2–0.4 mg
Butadiene	25–40 µg
Acetylene	20–35 µg
Benzene	12–50 µg
Toluene	20–60 µg
Styrene	10 µg
Other volatile aromatic hydrocarbons (29)	15–30 µg
Formic acid	200–600 µg
Acetic acid	300–1,700 µg
Propionic acid	100–300 µg
Methyl formate	20–30 µg
Other volatile acids (6)	5–10 µg[c]
Formaldehyde	20–100 µg
Acetaldehyde	400–1,400 µg
Acrolein	60–140 µg

TABLE 5.—Continued

Compound[a]	Concentration/cigarette
Other volatile aldehydes (6)	80–140 µg
Acetone	100–650 µg
Other volatile ketones (3)	50–100 µg
Methanol	80–180 µg
Other volatile alcohols (7)	10–30 µg[c]
Acetonitrile	100–150 µg
Other volatile nitriles (10)	50–80 µg[c]
Furan	20–40 µg
Other volatile furans (4)	45–125 µg[c]
Pyridine	20–200 µg
Picolines (3)	15–80 µg
3-Vinylpyridine	10–30 µg
Other volatile pyridines (25)	20–50 µg[c]
Pyrrole	0.1–10 µg
Pyrrolidine	10–18 µg
N-Methylpyrrolidine	2.0–3.0 µg
Volatile pyrazines (18)	3.0–8.0 µg
Methylamine	4–10 µg
Other aliphatic amines (32)	3–10 µg

[a]Numbers in parentheses represent individual compounds identified in a given group.
[b]Percent of total effluent.
[c]Estimate.
SOURCE: Hoffmann and Hecht (1989).

chemical nature and concentrations in cigarette smoke of agricultural chemicals and pesticides, which originate from the residues of such compounds in tobacco. There are many variations in the qualitative and quantitative aspects relative to such agents in tobacco from region to region and from year to year. Overall, the use of agricultural chemicals has also been greatly reduced (Wittekindt 1985). Nevertheless, it is fairly certain that commercial tobaccos contain up to a few parts per million of DDT, DDD,

TABLE 6.—Major constituents of the particulate matter of the mainstream smoke of nonfilter cigarettes

Compound[a]	µg/cigarette
Nicotine	1,000–3,000
Nornicotine	50–150
Anatabine	5–15
Anabasine	5–12
Other tobacco alkaloids (17)	NA
Bipyridyls (4)	10–30
n-Hentriacontane (n-$C_{31}H_{64}$)	100
Total nonvolatile hydrocarbons (45)[b]	300–400[b]
Naphthalene	2–4
Other naphthalenes (23)	3–6[b]
Phenanthrenes (7)	0.2–0.4[b]
Anthracenes (5)	0.05–0.1[b]
Fluorenes (7)	0.6–1.0[b]
Pyrenes (6)	0.3–0.5[b]
Fluoranthenes (5)	0.3–0.45[b]
Carcinogenic polynuclear aromatic hydrocarbons (11)[c]	0.1–0.25
Phenol	80–160
Other phenols (45)[b]	60–180[b]
Catechol	200–400
Other catechols (4)	100–200[b]
Other dihydroxybenzenes (10)	200–400[b]
Scopoletin	15–30
Other polyphenols (8)[b]	NA
Cyclotenes (10)[b]	40–70[b]
Quinones (7)	0.5
Solanesol	600–1,000

TABLE 6.—Continued

Compound[a]	µg/cigarette
Neophytadienes (4)	200–350
Limonene	30–60
Other terpenes (200–250)[b]	NA
Palmitic acid	100–150
Stearic acid	50–75
Oleic acid	40–110
Linoleic acid	60–150
Linolenic acid	150–250
Lactic acid	60–80
Indole	10–15
Skatole	12–16
Other indoles (13)	NA
Quinolines (7)	2–4
Other N-heterocyclic hydrocarbons (55)	NA
Benzofurans (4)	200–300
Other O-heterocyclic hydrocarbons (42)	NA
Stigmasterol	40–70
Sitosterol	30–40
Campesterol	20–30
Cholesterol	10–20
Aniline	0.36
Toluidines	0.23
Other aromatic amines (12)	0.25
Tobacco-specific N-nitrosamines (4)[c]	0.34–2.7
Glycerol	120

NOTE: NA, not available.
[a]Numbers in parentheses represent individual compounds identified in a given group.
[b]Estimate.
[c]See Table 7 for details.
SOURCE: Hoffmann and Hecht (1989).

and maleic hydrazide; fewer than 20 percent of these contaminants are transferred into the smoke stream.

The 1964 Surgeon General's Report listed five polynuclear aromatic hydrocarbons (PAHs) and three N-heterocyclic hydrocarbons as known carcinogenic smoke constituents (US PHS 1964). By the criteria for carcinogenicity of chemicals as set by the International Agency for Research on Cancer (1986), the carcinogens identified to date in tobacco smoke include 11 PAHs, 4 N-heterocyclic hydrocarbons, 9 N-nitrosamines, 3 aromatic amines, 3 aldehydes, 6 volatile carcinogens, 6 inorganic compounds, and the radioelement polonium-210 (Table 7; Hoffmann and Hecht 1989).

The Changing Cigarette

As discussed in Part I, epidemiologic studies have documented a dose–response relationship between the number of cigarettes smoked and the development of cancer of the lung, larynx, oral cavity, esophagus, pancreas, bladder, and kidney (US DHHS 1982; IARC 1986). Bioassays for tumorigenicity with whole smoke and with tar have also demonstrated a dose–response relationship (US DHHS 1982). As tar and nicotine yields in cigarette smoke gradually declined, other toxic and tumorigenic agents, such as CO, volatile N-nitrosamines, and carcinogenic PAHs, were also successfully reduced (Hoffmann, Tso, Gori 1980; Hoffmann et al. 1984; US DHHS 1981). However, it was soon realized that the smoker of low-yield cigarettes tended to compensate for reduced nicotine delivery by intensified smoking (US DHHS 1988), and therefore exposure may not actually have been lowered. Based on values generated by smoking machines under standardized conditions, Figure 14 shows the reduction in sales-weighted tar and nicotine delivery of the average U.S. cigarette. Arrows in the graph point to the introduction of technical changes in the manufacture of cigarettes at various times. These changes have influenced the machine-measured sales-weighted average nicotine and tar deliveries (Norman 1982). Technical issues in the machine measurements of delivered tar and nicotine yields also arose during 1982; modifications of the testing procedure were suggested (Federal Trade Commission 1984). The data shown in Figure 14 are based on the consistent testing procedures. Since 1981, the tar delivery of U.S. cigarettes has averaged between 13.0 and 12.7 mg, while nicotine delivery has remained stable at 0.9 mg per cigarette. (See Chapter 5, Table 26.) In the smoke of popular U.S. low-yield cigarettes, the reduction of nicotine, the primary pharmacologic factor in tobacco addiction (US DHHS 1988), has not occurred to the same extent as has the reduction of tar. The same development has been observed with cigarettes in the United Kingdom (Jarvis and Russell 1985).

Some modifications in the makeup of commercial cigarettes have led to a selective reduction of toxic and tumorigenic agents. Filter tips of cellulose acetate, the most common cigarette filter material, can selectively remove phenols and volatile N-nitrosamines from the smoke stream. Perforated filter tips selectively reduce CO and hydrogen cyanide (HCN) levels, and charcoal filters may selectively reduce volatile aldehydes and HCN. The incorporation into the tobacco blend of reconstituted tobacco sheets, expanded tobacco, and tobacco ribs has also contributed to a selective reduction of PAHs in cigarette smoke. The incorporation of ribs and stems and the utiliza-

TABLE 7.—Tumorigenic agents in tobacco and tobacco smoke

Compounds	Processed tobacco (per gram)	Mainstream smoke (per cigarette)	Evidence for IARC evaluation of carcinogenicity	
			In lab animals	In humans
PAH				
Benz(a)anthracene		20–70 ng	Sufficient	NA
Benzo(b)fluoranthene		4–22 ng	Sufficient	NA
Benzo(j)fluoranthene		6–21 ng	Sufficient	NA
Benzo(k)fluoranthene		6–12 ng	Sufficient	NA
Benzo(a)pyrene	0.1–90 ng	20–40 ng	Sufficient	Probable
Chrysene		40–60 ng	Sufficient	NA
Dibenz(a,h)anthracene		4 ng	Sufficient	NA
Dibenzo(a,i)pyrene		1.7–3.2 ng	Sufficient	NA
Dibenzo(a,l)pyrene		Present	Sufficient	NA
Indeno(1,2,3-c,d)pyrene		4–20 ng	Sufficient	NA
5-Methylchrysene		0.6 ng	Sufficient	NA
Aza-arenes				
Quinoline		1–2 µg	NA	NA
Dibenz(a,h)acridine		0.1 ng	Sufficient	NA
Dibenz(a,j)acridine		3–10 ng	Sufficient	NA
7H-Dibenzo(c,g)carbazole		0.7 ng	Sufficient	NA
N-Nitrosamines				
N-Nitrosodimethylamine	ND–215 ng	0.1–180 ng	Sufficient	NA
N-Nitrosoethyl methylamine		3–13 ng	Sufficient	NA
N-Nitrosodiethylamine		ND–25 ng	Sufficient	NA
N-Nitrosopyrrolidine	ND–360 ng	1.5–110 ng	Sufficient	NA
N-Nitrosodiethanolamine	ND–6,900 ng	ND–36 ng	Sufficient	NA
N′-Nitrosonornicotine	0.3–89 µg	0.12–3.7 µg	Sufficient	NA
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone	0.2–7 µg	0.08–0.77 µg	Sufficient	NA
N′-Nitrosoanabasine	0.01–1.9 µg	0.14–4.6 µg	Limited	NA
N-Nitrosomorpholine	ND–690 ng		Sufficient	NA

TABLE 7.—*Continued*

Compounds	Processed tobacco (per gram)	Mainstream smoke (per cigarette)	Evidence for IARC evaluation of carcinogenicity	
			In lab animals	In humans
Aromatic amines				
2-Toluidine		30–200 ng	Sufficient	Inadequate
2-Naphthylamine		1–22 ng	Sufficient	Sufficient
4-Aminobiphenyl		2–5 ng	Sufficient	Sufficient
Aldehydes				
Formaldehyde[a]	1.6–7.4 µg	70–100 µg[a]	Sufficient	NA
Acetaldehyde[a]	1.4–7.4 mg	18–1,400 mg[a]	Sufficient	NA
Crotonaldehyde	0.2–2.4 µg	10–20 µg	NA	NA
Miscellaneous organic compounds				
Benzene		12–48 µg	Sufficient	Sufficient
Acrylonitrile		3.2–15 µg	Sufficient	Limited
1, 1-Dimethylhydrazine	60–147 µg		Sufficient	NA
2-Nitropropane		0.73–1.21 µg	Sufficient	NA
Ethylcarbamate	310–375 ng	20–38 ng	Sufficient	NA
Vinyl chloride		1–16 ng	Sufficient	Sufficient
Inorganic compounds				
Hydrazine	14–51 ng	24–43 ng	Sufficient	Inadequate
Arsenic	500–900 ng	40–120 ng	Inadequate	Sufficient
Nickel	2,000–6,000 ng	0–600 ng	Sufficient	Limited
Chromium	1,000–2,000 ng	4–70 ng	Sufficient	Sufficient
Cadmium	1,300–1,600 ng	41–62 ng	Sufficient	Limited
Lead	8–10 µg		Sufficient	Inadequate
Polonium-210	0.2–1.2 pCi	0.03–1.0 pCi	NA	NA

NOTE: ND, no data; NA, evaluation has not been done by IARC.

[a]The Fourth Report of the Independent Scientific Committee on "Smoking and Health" (1988) published values for the 14 leading U.K. cigarettes in 1986 (51.4 percent of the market) of 20–105 µg/cigarette (mean, 59 µg) for formaldehyde and 550–1,150 µg/cigarette (mean, 910 µg) for acetaldehyde.

SOURCE: Hoffmann and Hecht (1989).

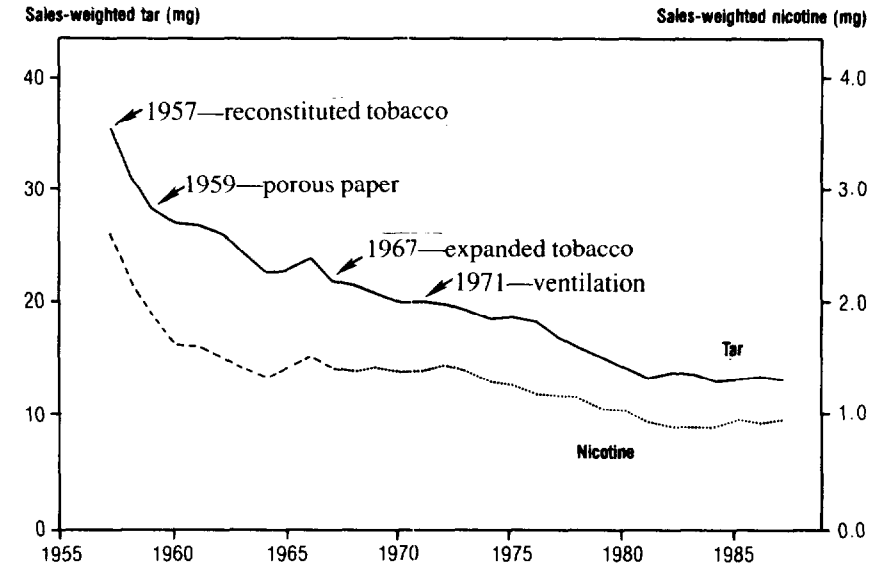

FIGURE 14.—"Tar" and nicotine content of U.S. cigarettes, sales-weighted average basis, 1957–87

NOTE: Nicotine values for 1957–67 are estimates.

SOURCE: 1957–67, Wakeham (1976), fourth-quarter estimates for each year; 1968–81, FTC (1984); 1982–87, derived from FTC data tape of annual cigarette company submissions to the FTC. This database is the same as that used for the ongoing FTC tobacco report series. Since 1981, these reports have not listed the sales-weighted tar average. Historical events are noted in R. J. Reynolds (1988).

tion of more burley varieties in the tobacco blend have led to an increase in the nitrate content of the U.S. blended cigarette from 0.5 percent to between 1.2 to 1.5 percent. This development brought about a reduction of the smoke yields of tar, phenols, and PAHs, but has caused an increase of the nitrogen oxides in the smoke and thus has increased the potential for N-nitrosamine formation (US DHHS 1981, 1982; Hoffmann et al. 1984). The development of the low-yield cigarette has also necessitated an enrichment of the flavor "bouquet" in the smoke either by tobacco selection or by addition of natural or synthetic flavor compounds. These facts and the practice of smoking low-yield cigarettes more intensely make it difficult to evaluate whether these new types of cigarettes are in fact less hazardous to the smoker (see Chapter 8). Changes in the market share of filtered cigarettes, lower yield cigarettes, mentholated cigarettes, and longer cigarettes are presented in Chapter 5.

Environmental Tobacco Smoke

SS is the smoke generated during smoldering of tobacco products between puffs. When it is obtained under standard laboratory conditions, undiluted SS contains far higher amounts of toxic and tumorigenic agents than MS, which is drawn puff by puff through the unlit end of the cigarette. Table 8 presents data for those toxic agents in SS that are known carcinogens, tumor promoters, and cocarcinogens. The release of volatile N-nitrosamines and aromatic amines into the SS is remarkably higher than that into MS (US DHHS 1988; Guerin 1987). Whereas filter tips, especially perforated

TABLE 8.—Some toxic and tumorigenic agents in undiluted cigarette sidestream smoke

Compound	Type of toxicity	Amount in sidestream smoke (per cigarette)	Amount in sidestream smoke/ amount in mainstream smoke
Vapor phase			
Carbon monoxide	T	26.8–61 mg	2.5–14.9
Carbonyl sulfide	T	2–3 µg	0.03–0.13
Benzene	C	400–400 µg	8–10
Formaldehyde	C	1,500 µg	50
3-Vinylpyridine	SC	300–450 µg	24–34
Hydrogen cyanide	T	14–110 µg	0.06–0.4
Hydrazine	C	90 ng	3
Nitrogen oxides (NO_x)	T	500–2,000 µg	3.7–12.8
N-Nitrosodimethylamine	C	200–1,040 ng	20–130
N-Nitrosopyrrolidine	C	30–390 ng	6–120
Particulate phase			
Tar	C	14–30 mg	1.1–15.7
Nicotine	T	2.1–46 mg	1.3–21
Phenol	TP	70–250 µg	1.3–3.0
Catechol	CoC	58–290 µg	0.67–12.8
o-Toluidine	C	3 µg	18.7
2-Naphtylamine	C	70 ng	39
4-Aminobiphenyl	C	140 ng	31
Benz(a)anthracene	C	40–200 ng	2–4
Benzo(a)pyrene	C	40–70 ng	2.5–20
Quinoline	C	15–20 µg	8–11
NNN	C	0.15–1.7 µg	0.5–5.0
NNK	C	0.2–1.4 µg	1.0–22
N-Nitrosodiethanolamine	C	43 ng	1.2
Cadmium	C	0.72 µg	7.2
Nickel	C	0.2–2.5 µg	13–30
Polonium-210	C	0.5–1.6 pCi	1.06–3.7

NOTE: C, carcinogenic; CoC, cocarcinogenic; SC, suspected carcinogen; T, toxic; TP, tumor promoter; NNN, N′-Nitrosonornicotine; NNK, 4-(methylnitrosamino)-(3-pyridyl)-1-butanone.
SOURCE: Hoffmann and Hecht (1989).

ones, can significantly reduce the concentration of toxic and tumorigenic agents in MS, they have no reducing effect on the agents emitted into the SS (Adams, O'Mara-Adams, Hoffmann 1987).

SS is the major source of ETS. The smoke diffusing through the cigarette paper, the smoke emerging from the burning cone during active smoking, and that portion of MS that is exhaled also contribute to ETS. Table 9 presents some data for toxic agents resulting from tobacco combustion in indoor environments (US DHHS 1988; Hoffmann and Hecht 1989). The concentrations of toxic agents in ETS appear low in comparison with their levels in undiluted cigarette MS. With regard to exposure factors, one needs to take into account the fact that the active inhalation of MS is limited to the time it takes to smoke each cigarette, whereas the inhalation of ETS is constant over several hours spent in the polluted environment. This is reflected in the results of measurements of the uptake of nicotine by active and passive smokers (US DHHS 1988).

Smokeless Tobacco

As noted above, the special Report of the Surgeon General, *The Health Consequences of Using Smokeless Tobacco*, has shown that tobacco chewers and snuff dippers face an increased risk for cancer of the oral cavity (US DHHS 1986b). In the United States the four primary smokeless tobacco types are plug tobacco, loose leaf tobacco, twist tobacco, and snuff.

The composition of processed, unadulterated tobacco has been discussed. Chewing tobacco and snuff are made with various flavor additives (LaVoie et al. 1989). It is of special significance that the preparation of smokeless tobacco products, which entails curing, fermentation, and aging, occurs under conditions favoring the formation of tobacco-specific N-nitrosamines (TSNAs) from nicotine and other tobacco alkaloids such as nornicotine, anatabine, and anabasine (Figure 15). Of the six identified TSNAs in smokeless tobacco, N′-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) are strong carcinogens in mice, rats, and hamsters, inducing benign and malignant tumors of the oral cavity, nasal cavity, esophagus, lung, liver, and pancreas (Hecht and Hoffmann 1988; Rivenson et al. 1988). Table 10 presents chemical–analytical data for TSNAs in U.S. smokeless tobacco products (Hoffmann and Hecht 1988). The concentrations of carcinogenic nitrosamines in smokeless tobacco exceed those in other consumer products by at least 2 orders of magnitude (US DHHS 1986b). During tobacco chewing and snuff dipping, additional amounts of carcinogenic TSNAs are most likely also formed endogenously in the oral cavity (Hoffmann and Hecht 1988). Carcinogenic TSNAs have been regarded as a major factor for the association of snuff-dipping with oral cancer in humans (Craddock 1983).

Other carcinogens identified in smokeless tobacco are volatile nitrosamines (N-nitrosodimethylamine, ≤215 ppb), N-nitrosomorpholine (≤40 ppb), N-nitrosodiethylamine (≤6,800 ppb), formaldehyde (≤7,000 ppb), crotonaldehyde (≤2,400 ppb), and benzo(*a*)pyrene (≤90 ppb), as well as traces of the radioelement polonium-210 (≤0.6 pCi/g) (US DHHS 1986; Hoffmann et al. 1987; Chamberlain, Schlotzhauer, Chortyk 1988).

TABLE 9.—Some toxic and tumorigenic agents in indoor environments polluted by tobacco smoke

Pollutant	Location	Concentration/m^3
Nitric oxide	Workrooms	50–440 µg
	Restaurants	17–270 µg
	Bars	80–520 µg
	Cafeterias	2.5–48 µg
Nitrogen dioxide	Workrooms	68–410 µg
	Restaurants	40–190 µg
	Bars	2–116 µg
	Cafeterias	67–200 µg
Hydrogen cyanide	Living rooms	8–122 µg
Benzene	Public places	20–317 µg
Formaldehyde	Living rooms	23–50 µg
Acrolein	Public places	30–120 µg
Acetone	Public places	360–5,800 µg
Phenols (volatile)	Coffee houses	7.4–11.5 ng
N-Nitrosodimethylamine	Restaurants, public places	0–240 ng
N-Nitrosodiethylamine	Restaurants, public places	0–200 ng
Nicotine	Public places	1–6 µg
	Restaurants	3–10 µg
	Workrooms	1–13.8 µg
Benzo(a)pyrene	Restaurants, public places	3.3–23.4 ng

SOURCE: Hoffmann and Hecht (1989).

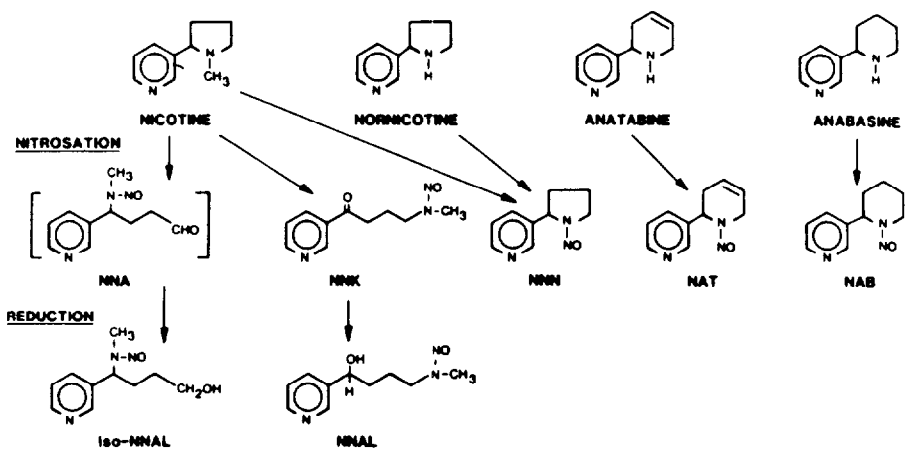

FIGURE 15.—Formation of tobacco-specific N-nitrosamines

TABLE 10.—Tobacco-specific N-nitrosamines in U.S. smokeless tobacco (ppb)

Product	NNN	NNK	NAT	NAB
Loose leaf tobacco	670–8,200 (6[a])	380 (1)	2,300 (1)	140 (1)
Plug tobacco	3,400–4,300 (3)			
Snuff—moist	3,120–135,000 (26)	100–13,600 (25)	1,340–339,000 (20)	10–6,700 (16)
Snuff—dry	9,000–52,000 (3)	1,800–13,000 (3)	18,000–38,000 (3)	60–60,000 (3)

NOTE: NNN, N′-Nitrosonornicotine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NAT, N′-nitrosoanatabine; NAB, N′-nitrosoanabasine.

[a]Number in parentheses is the number of samples analyzed.

SOURCE: Hoffmann and Hecht (1988).

Toxicity and Carcinogenicity of Tobacco Smoke

Undiluted tobacco smoke is too toxic to be tolerated by laboratory animals primarily because of the acute toxic effects of CO. CO in cigarette smoke increases with ascending puff number from 2 to 5 volume percent (the average CO content of cigarette smoke is 3.5 to 4.5 volume percent). The acute toxicity of tobacco smoke is also due to HCN, nicotine, and volatile aldehydes. In vitro short-term exposure to cigarette smoke causes ciliastasis, an effect primarily attributable to HCN (300 to 500 µg/cigarette) and volatile aldehydes (500 to 2,000 µg/cigarette). The long-term exposure of laboratory animals to diluted cigarette smoke causes impairment of mucociliary

clearance, mucus hypersecretion, and epithelial lesions. Cigarette smoke constituents responsible for this effect are both the gas phase, primarily HCN and volatile aldehydes, and the particulate phase (US DHEW 1979; US DHHS 1984).

Long-term inhalation of diluted cigarette smoke by mice has resulted in adenomas and adenocarcinomas of the lung, whereas such inhalation in rats has only led to a few isolated tumors of the lung. In Syrian golden hamsters, long-term smoke inhalation studies have regularly induced benign and malignant tumors of the larynx and only a few lung tumors. These observations strongly suggest, and studies of particulate deposition and determination of carboxyhemoglobin (COHb) and nicotine–cotinine in the blood of the smoke-exposed animals have confirmed, that laboratory animals do not inhale the smoke deeply. Intratracheal instillation of cigarette tar and one of its fractions has resulted in lung tumors, including bronchogenic carcinomas (Mohr and Reznik 1978; Dalbey et al. 1980; US DHHS 1982).

The particulate matter (more often called "tar") suspended in organic solvents has induced carcinoma in the rat after subcutaneous injection and benign and malignant tumors in the skin of mice and rabbits after topical application. The major tumor initiators reside in the PAH-enriched neutral subfractions, whereas the tumor promoters and cocarcinogens are found in the weakly acidic fraction as well as in the polaric neutral subfraction (Wynder and Hoffmann 1967; Mohr and Reznik 1978; US DHHS 1982; Hoffmann and Hecht 1988).

As discussed earlier, combined chemical–analytical studies have led to the identification of several organ-specific carcinogens in cigarette smoke. The diversity of these carcinogens and those identified as contact carcinogens may cause ambiguity as to which among them are most important. Table 11, which is based on extensive laboratory studies, lists the likely causative agents associated with the increased risk of cigarette smokers for cancer of the various organs (Hoffmann and Hecht 1988).

Nicotine

It is generally held that nicotine is the active pharmacologic agent in tobacco that determines the addictive behavior of the tobacco smoker (US DHHS 1988). Nicotine, together with CO, is also regarded as a major contributor to cigarette smokers' increased risk of cardiovascular disease (US DHHS 1983, 1988). In addition to nicotine, tobacco contains various other alkaloids, most of which are 3-pyridyl derivatives. In the blended U.S. cigarette, nicotine constitutes 85 to 95 percent of the total alkaloids. During the smoking of a nonfilter cigarette, about 15 percent of the nicotine appears in the MS, 35 to 40 percent appears in the SS, 15 to 20 percent is deposited in the butt, and the remainder is broken down into pyrolysis products. The major pyrolysis products of nicotine are CO, carbon dioxide, 3-vinylpyridine, 3-methylpyridine, pyridine, myosmine, and 2,3′-dipyridyl (US DHHS 1982).

As discussed earlier, the absorption of nicotine from tobacco smoke is pH dependent. When tobacco smoke reaches the small airways and alveoli of the lung, nicotine is rapidly absorbed. In chewing tobacco and snuff with their alkaline pH, nicotine is primarily absorbed through the mucous membranes of the oral cavity. Nicotine enters the blood and is rapidly transported to the brain, which has specific receptor sites for

TABLE 11.—Likely causative agents for tobacco-related cancers

Organ	Initiator or carcinogen	Enhancing agents
Lung, larynx	PAH	Catechol (cocarcinogen) Weakly acidic tumor promoters
	NNK	Acrolein, crotonaldehyde (?)
	Polonium-210 (minor factor), acetaldehyde, formaldehyde	
Esophagus	NNN	
Pancreas	NNK(?)	
Bladder	4-Aminobiphenyl 2-Naphthylamine	
Oral cavity (smoking)	PAH NNK, NNN	Ethanol
Oral cavity (snuff dipping)	NNK, NNN	Irritation (?) Herpes simplex (?)
	Polonium-210	

NOTE: PAH, polynuclear aromatic hydrocarbons; NNK, 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone; NNN, N′-Nitrosonornicotine.
SOURCE: Hoffmann and Hecht (1989).

the drug. The effects of nicotine on the central nervous system are associated with the development of tobacco dependence (US DHHS 1988).

Nicotine is metabolized primarily in the liver and, to a smaller extent, in the lung. About 10 to 15 percent of the absorbed nicotine is excreted unchanged in the urine. The primary metabolites of nicotine are cotinine and nicotine-N′-oxide. Cotinine is further metabolized extensively, with only 17 percent of it appearing unchanged in the urine (Benowitz 1986; Neurath et al. 1987; US DHHS 1988). Cotinine measurements in saliva, serum, or urine serve as an indicator for nicotine uptake by tobacco chewers, active smokers, and involuntary smokers. It takes 18 to 20 hr to eliminate one-half of the cotinine present in an active smoker through renal excretion; an involuntary smoker shows a considerably slower rate of elimination (Sepkovic, Haley, Hoffmann 1986; US DHHS 1988).

Biological Markers

Techniques for the determination of current and lifetime exposures to tobacco products include the examination of medical records and data from prospective and

case–control studies as well as the utilization of biological markers. The development of highly sensitive and reproducible methods has led to increased use of biological markers for uptake of tobacco smoke constituents.

Table 12 lists those biochemical markers that are currently used to determine exposure to tobacco smoke components after active inhalation of MS and also after involuntary uptake of ETS. Some of these markers are also the basis for measuring the transfer of smoke constituents from the maternal bloodstream to a developing fetus.

The tobacco-specific alkaloid nicotine and its major metabolite, cotinine, are most frequently used as serum and urine indicators of the uptake of tobacco smoke by active smokers and also to indicate ETS exposure in nonsmokers. Unlike CO, nicotine is not

TABLE 12.—Biochemical markers for the uptake of tobacco smoke

Smoke constituent	Biochemical marker	Substrate	Method	Sensitivity	Critical value[a]
Nicotine	Nicotine	Serum Urine	GC	1 ng/mL	0
		Serum Urine	RIA	0.2 ng/mL	0
	Cotinine	Saliva Serum Urine	GC	5 ng/mL	0
		Saliva Serum Urine	RIA	1 ng/mL	0
Carbon monoxide (CO)	COHb	Blood	Oximeter	±0.1%	0.9 ±0.7%
	CO	Exhaled air	GC	±1 ppm	5.6 ±2.7 ppm
Hydrogen cyanide (HCN)	Thiocyanate (SCN^-)	Saliva Serum Urine	Autoanalyzer (color reaction)	±5 µmol/L	100 µmol/L
Nitrogen oxides (NO_x)	Nitrosoproline	Urine	GC/TEA	±0.4 µg/L	2.0 ±1.5 µg/24 hours
Ethylene ($CH_2=CH_2$)	Globin-adduct	Blood	GC	±5pmol/gHb	58 ±25 pmol/gHb
4-Aminobiphenyl	Globin-adduct	Blood	GC	?	<70 pg/gHb
Tobacco-specific nitrosamines	Globin-adduct	Blood	GC	?	Not established

[a]Critical values, values measured in nonsmokers.

SOURCE: International Agency for Research on Cancer (1987).

only taken up by inhalation but also is absorbed through the mucous membranes in the oral cavity. Therefore, it is possible to determine user uptake of hydrophilic agents from chewing tobacco and snuff by means of nicotine–cotinine measurements. The analytical assessment of nicotine and cotinine in physiological fluids is done primarily by gas chromatography and radioimmunoassay (IARC 1986). Both methods are highly sensitive (between 0.2 and 5 ng/mL), and there is little or no interference by other smoke components. After environmental exposure, the average nicotine and cotinine levels in saliva, plasma, and urine of nonsmokers vary from 0.5 to 4.0 μg/mL, whereas the average amount of nicotine in the serum of cigarette smokers ranges from 15 to 40 μg/mL and lies between 500 and 2,000 μg/mL in saliva and urine. Cotinine concentration varies from 150 to 350 μg/mL in plasma, from 150 to 400 μg/mL in saliva, and can go up to 2,000 μg/mL in urine (Jarvis et al. 1984; US DHHS 1988). In snuff dippers and tobacco chewers, plasma nicotine levels were found between 3 to 22 μg/mL and plasma cotinine was 200 to 400 μg/mL (US DHHS 1986).

One of the oldest methods for estimating the inhalation of tobacco smoke is the determination of COHb in blood. Since some CO is endogenously formed, the background values for COHb in the blood of nonsmokers without occupational exposure to CO range from 0.5 to 1.5 percent (National Research Council 1977). Smoking only a few cigarettes per day elevates COHb levels to 2.0 percent. In a study of men aged 34 to 64 years, cigarette smokers had average COHb concentrations of 4.7 percent; cigar smokers, 2.9 percent; and pipe smokers, 2.2 percent (Wald et al. 1981; Wald and Ritchie 1984). The COHb values of nonsmokers after ETS exposure do not markedly exceed 1.5 percent; thus, COHb cannot serve as an indicator of exposure to ETS (NRC 1986). Since CO is only slowly released from the blood in the process of exhaling, the smoking intensity of a cigarette smoker can also be assessed by the analysis of CO in the exhaled breath. The critical value for CO, the value above that of a nonsmoker, is 5.6±2.7 ppm in exhaled breath; again this method is not applicable to the dosimetry of nonsmoker ETS exposures.

HCN, a major tobacco smoke constituent (>100 μg/cigarette), is absorbed upon inhalation and is detoxified in the liver, yielding SCN^-. Since SCN^- can also originate from dietary intake, only values above 100 μmol of SCN^- per L of serum as measured for cigarette smokers are meaningful for dosimetry of uptake. In general, the average cigarette smoker has SCN^- levels between 100 and 250 μmol/L of serum (US DHHS 1987).

A number of studies have clearly demonstrated that the mutagenic activity of the urine of cigarette smokers is higher than that of nonsmokers (IARC 1986). The most widely applied method for determining mutagenic activity of urine samples was developed by Yamasaki and Ames (1977), using a resin to concentrate the body fluid and, upon metabolic activation, measuring the mutagenic activity on bacterial tester strains TA98 and TA1538. In general, the urine of cigarette smokers exhibits at least twice the mutagenic activity of that measured in nonsmokers' urine.

In summary, there are several biochemical indicators that enable investigators to assay the uptake of tobacco smoke by individuals or by groups of individuals. Whereas analyses of exhaled CO, of COHb, and of SCN^- and nicotine–cotinine in saliva, serum, and urine are well suited for determining the smoking intensity of an active smoker,

only nicotine and cotinine determinations in serum and urine can also serve as indicators for the exposure of nonsmokers to ETS.

Summary

The 1964 Surgeon General's Report was a landmark study that reviewed and assessed the available epidemiologic, clinical, pathological, and experimental literature for evidence linking cigarette smoking to disease. The principal findings of that Report are summarized in Table 13. In men, cigarette smoking was found to increase overall mortality and to cause lung and laryngeal cancer. Several other important conclusions were also drawn (Table 13).

Since 1964, 20 reports of the Surgeon General (including this Report) have been released on tobacco and health that substantiate and strengthen the original conclusions of the 1964 Report. These reports have also established associations between smoking and disease in areas for which data did not exist, shed light on pathogenetic mechanisms of tobacco-related disease, and added scientific depth to areas mentioned only briefly in the 1964 Report.

A review of Table 13 allows the reader to survey quickly the state of knowledge on cigarette smoking and health in 1989 and to compare it with what was known in 1964. Of the 27 principal effects presented in Table 13, 13 were first noted in 1964; among those 13 effects, many have been strengthened since 1964. Recent reports of the Surgeon General have also covered important topics not even mentioned in the 1964 Report. For example, these reports have concluded that involuntary smoking can cause disease, including lung cancer, in healthy nonsmokers and that smokeless tobacco can cause oral cancer. The most recent Surgeon General's Report also concluded that the use of cigarettes and other forms of tobacco is addicting (US DHHS 1988).

Much progress has been made in understanding the physicochemical nature of tobacco smoke. Today, the estimated number of compounds in tobacco smoke exceeds 4,000, including some that are pharmacologically active, toxic, mutagenic, or carcinogenic. The diverse biological effects of tobacco smoke constituents provide a framework for understanding the multiple adverse consequences of smoking. For example, the identification of 43 different carcinogenic substances in tobacco smoke helps explain why cigarette smoking can cause cancer at different sites including the lung, larynx, oral cavity, and esophagus; why cigarette smoking is a contributory factor for the development of cancer at different sites including the bladder, kidney, and pancreas; and why cigarette smoking is associated with cancer of the stomach and uterine cervix.

The central role of cigarette smoking as a massive, preventable personal and public health problem can now be better appreciated. In the United States, it is a major cause of CHD, this country's most common cause of death; cigarette smoking is estimated to account for 21 percent of all CHD deaths. Cigarette smoking is the major cause of lung cancer, the most common cause of cancer death in the United States; smoking is estimated to account for 87 percent of lung cancer deaths and 30 percent of all cancer deaths. While lung cancer death rates for women who are nonsmokers have not increased since the early 1960s, comparable death rates for women who smoke cigarettes have increased more than fourfold. In 1986, lung cancer and breast cancer were the

TABLE 13.—Summary of the principal effects of cigarette smoking

Effect first discussed in Surgeon General's Reports	Year first discussed in a Surgeon General's Report	Current knowledge in 1989
Mortality and morbidity		
Overall mortality, increased in men	1964	Overall mortality increased in men and women
Overall morbidity, increased	1967	Overall morbidity increased
Cardiovascular		
CHD, mortality increased in men	1964	A major cause of coronary heart disease in men and women
Cerebrovascular disease (stroke), mortality increased	1964	A cause of cerebrovascular disease (stroke)
Atherosclerotic aortic aneurysm, mortality increased	1967	Increased mortality from atherosclerotic aortic aneurysm
Atherosclerotic peripheral vascular disease, risk factor	1971	A cause and most important risk factor for atherosclerotic peripheral vascular disease
Cancer		
Lung cancer, the major cause in men	1964	The major cause of lung cancer in men and women
Laryngeal cancer, a cause in men	1964	The major cause of laryngeal cancer in men and women
Oral cancer (lip), a cause (pipe smoking)	1964	A major cause of cancer of the oral cavity (lip, tongue, mouth, pharynx)
Esophageal cancer, associated with	1964	A major cause of esophageal cancer
Bladder cancer, associated with	1964	A contributory factor for bladder cancer
Pancreatic cancer, increased mortality	1967	A contributory factor for pancreatic cancer
Renal cancer, increased mortality	1968	A contributory factor for renal cancer
Gastric cancer, associated with	1982	An association with gastric cancer
Cervical cancer, possible association with	1982	An association with cervical cancer

TABLE 13.—Continued

Effect first discussed in Surgeon General's Reports	Year first discussed in a Surgeon General's Report	*Current knowledge in 1989*
Pulmonary		
Chronic bronchitis, the major cause	1964	The major cause of chronic bronchitis
Emphysema, increased mortality	1964	The major cause of emphysema
Women		
Low-birthweight babies, associated with	1964	A cause of intrauterine growth retardation
Unsuccessful pregnancy, associated with	1980	A probable cause of unsuccessful pregnancies
Other effects		
Tobacco habit, related to psychological and social drives	1964	Cigarette smoking and other forms of tobacco use are addicting
Involuntary smoking, irritant effect	1972	A cause of disease, including lung cancer, in healthy nonsmokers
Peptic ulcer disease, associated with	1964	A probable cause of peptic ulcer disease
Occupational interactions, adverse	1971	Adverse occupational interactions that increase the risk of cancer
Alcohol interactions, adverse	1971	Adverse interactions with alcohol that increase the risk of cancer
Drug interactions, adverse	1979	Adverse drug interactions
Nonmalignant oral disease, associated with	1969	An association with nonmalignant oral disease
Smokeless tobacco, associated with oral cancer	1979	Smokeless tobacco is a cause of oral cancer

leading causes of cancer death in U.S. women, accounting for approximately equal numbers of cancer deaths. Cigarette smoking is the major cause of COPD, an effect that far outweighs all other factors; smoking is estimated to account for 82 percent of COPD deaths. (See Chapter 3.)

The 1964 Report of the Surgeon General stated that death rates from cerebrovascular disease (stroke) were increased in cigarette smokers compared with nonsmokers, but it drew no conclusions concerning causality. In the current 1989 Report, for the first time, cigarette smoking is cited as a cause of stroke, the third most common cause of death in the United States. Stopping smoking reduces the risk of stroke.

The effect of smoking on pregnancy was briefly mentioned in the 1964 Report. Many studies have subsequently shown that cigarette smoking causes fetal growth retardation and is a probable cause of unsuccessful pregnancies.

Table 13 summarizes other important smoking associations with several diseases, including atherosclerotic aortic aneurysm, atherosclerotic peripheral vascular disease, and peptic ulcer disease; it also includes occupational and alcohol-related interactions with smoking that increase the risk of cancer.

Finally, the reports of the Surgeon General have emphasized the benefits of quitting for smokers of all ages.

CONCLUSIONS

Part I. Health Consequences

1. The 1964 Surgeon General's Report concluded that cigarette smoking increases overall mortality in men, causes lung and laryngeal cancer in men, and causes chronic bronchitis. The Report also found significant associations between smoking and numerous other diseases.
2. Reports of the Surgeon General since 1964 have concluded that smoking increases mortality and morbidity in both men and women. Disease associations identified as causal since 1964 include coronary heart disease, atherosclerotic peripheral vascular disease, lung and laryngeal cancer in women, oral cancer, esophageal cancer, chronic obstructive pulmonary disease, intrauterine growth retardation, and low-birthweight babies.
3. Cigarette smoking is now considered to be a probable cause of unsuccessful pregnancies, increased infant mortality, and peptic ulcer disease; to be a contributing factor for cancer of the bladder, pancreas, and kidney; and to be associated with cancer of the stomach.
4. Accumulating research has elucidated the interaction effects of cigarette smoking with certain occupational exposures to increase the risk of cancer, with alcohol ingestion to increase the risk of cancer, and with selected medications to produce adverse effects.
5. A decade ago, the 1979 Report of the Surgeon General found smokeless tobacco to be associated with oral cancer. In 1986, the Surgeon General concluded that smokeless tobacco was a cause of this disease.